# The Pathogenesis of Gastric Ulcer *

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THE IDEA that gastric and duodenal ulcers are caused by the digestant action of the gastric juice developed from the realization that these lesions occur only in those regions of the gastro-intestinal tract that come into contact with the gastric secretion. In 1920 Arthur Hurst[24] summarized this prevailing view in the following statement.

"An ulcer of the peculiar type found in the stomach occurs nowhere else in the body except the first part of the duodenum and the part of the jejunum immediately adjoining the stoma of a gastroenterostomy. The one common feature of these three situations is the presence of gastric juice. But gastric juice will not digest the normal mucous membrane."

As will become evident, the latter part of this statement is incorrect, but while the idea dominated men's minds it seemed necessary to postulate that in patients with peptic ulcer a local decrease in the resistance of an area of the mucosa must precede the digestion of the tissue. In the intervening years it has been suggested that this decrease in resistance is brought about by thrombosis or embolism due to arteriosclerosis in the terminal branches of the gastric or duodenal arteries, as proposed by Virchow and Hauser, by local vascular spasm, by local allergy, by decrease in the anti-enzyme content of the cells, by deficiency of protective mucus or by general debility of the mucosa cells as a result of anemia, malnutrition, or specific vitamin deficiency.

However, there is little evidence to indicate that a local decrease in the vitality of the gastric or duodenal mucosa, even to complete necrosis, would cause a chronic peptic ulcer if the corrosive properties of the gastric content are within the normal range. When partial gastrectomy for the treatment of peptic ulcer became popular, Konjetzny[21] and many others examined the gastric and duodenal blood vessels in large numbers of resected specimens but failed to find evidence of local arteriosclerosis, thrombosis or embolism. In the experimental laboratory it was found that even extensive ligation of the blood vessels to the stomach did not produce lesions in the mucosa because of the abundant collateral circulation. When the critical point was exceeded, large portions of the stomach became gangrenous, but chronic progressive peptic ulcers were not produced. A similar result has been recorded in man[38] and also when the blood supply to the stomach has been too greatly reduced in the effort to extend it high in the chest after resections of the esophagus for carcinoma. Here again, when the critical point has been exceeded, necrosis of the stomach rather than peptic ulceration has resulted. In the surgical treatment of gastric and duodenal ulcers, local excision of the lesions, with some ancillary procedure, was tried but found to be ineffective. New ulcers appeared in other areas. If the essential defect causing the ulcer was local thrombosis or embolism, excision of the involved area should have given a better

result. Duodenal ulcers occur predominantly in young and otherwise healthy adult men in whom evidence of arteriosclerosis, malnutrition, vitamin deficiency, or other systemic disease is not conspicuous. On the other hand, older people who do have arteriorsclerosis rarely have ulcers in the duodenum.

In the laboratory, attempts to demonstrate that local necrosis of an area of gastric or duodenal mucosa will produce a chronic peptic ulcer have invariably failed. In experiments on dogs, the senior author has excised circular areas of the gastric mucosa two centimeters in diameter or destroyed similar areas with the cautery or with chemicals and then placed these animals on the usual coarse laboratory diets. Within a few days a sharply punched out acute lesion appeared in the involved area, but invariably healed completely in a period of six to eight weeks. The normal gastric content of dogs is relatively innocuous to living tissue, and clinical experience suggests that the same is true in man. The fears of Billroth that surgical wounds in the stomach would fail to heal because of the presence of gastric juice, were shortly proved to be groundless.

It should perhaps be emphasized that acute lesions resembling peptic ulcers can be produced in the stomach and duodenum of experimental animals in a wide variety of ways, but these have little relevance for the problem of peptic ulcer in man unless chronicity, characterized by progression, hemorrhage and perforation, also results. For these reasons, among others, it is exceedingly doubtful that a local decrease in resistance of the mucosa can account for any large number of the peptic ulcers seen in man.

Although the normal gastric content is not significantly injurious, experimental studies have demonstrated that the pure undiluted gastric juice is an exceedingly corrosive fluid and can destroy and digest all living tissues, including the mucosa of the intestines and of the stomach itself. It now seems curious that the older workers failed to make this distinction between gastric content and gastric juice. The gastric content consists not only of gastric juice, but also of various amounts of swallowed food and saliva, mucus from the pyloric antrum, and regurgitated duodenal secretions, all of which exert a protective effect by buffering and diluting the gastric secretion. When these protective substances are present in insufficient amounts or when an excessive secretion of gastric juice occurs, the gastric content approximates the pure fundic secretion in its corrosive properties. Under these conditions the mucosa succumbs, an acute ulcer forms, and this becomes the chronic progressive peptic ulcer because of continued contact with the abnormally corrosive gastric content. These facts were made evident by a long series of experimental studies on lower animals, of which only a few need to be alluded to here.

Exalto[16] and Mann and Williamson[31] first produced chronic duodenal ulcers in animals fulfilling the criteria referred to above by draining the alkaline juices of the duodenum into the lower ileum. They attributed these ulcers to an increase in the corrosive properties of the gastric content which entered the duodenum because of the absence of the automatic neutralizing effect of the pancreatic juice and bile. However, in these preparations the acid gastric chyme fails to enter the duodenum and the usual inhibition of gastric secretion which results from the passage of acid into the duodenum is absent.[33] As a result, an excessive secretion of gastric juice occurs[39] sufficient in itself to produce a chronic peptic ulcer. Hay, Varco, Code and Wangensteen[13] succeeded in producing a long continued hypersection of gastric juice in animals by implanting pellets of histamine and beeswax into the subcutaneous tissues and muscles. Typical chronic gastric and duodenal ulcers resulted. Perhaps the clear-

est demonstration of the destructive power of pure undiluted gastric juice is the appearance of gastric ulcers in vagus innervated total stomach pouches [13] and of chronic peptic ulcers in the small intestines of dogs when the gastric juice from a Pavlov or Heidenhain pouch has been drained into the ileum or jejunum instead of to the exterior.[32] These latter lesions are the experimental counterpart of the Meckel's diverticulum ulcers in human pathology.[1, 29]

While there can be no doubt that mucus and the anatomic folds of the gastric mucosa help to protect it from peptic digestion, these factors are less important than dilution and neutralization of the gastric juice by food. In 1924 Dragstedt and Vaughn [11] found that organs such as the spleen and kidney were not digested away if implanted into defects made in the gastric wall of dogs and subjected to the digestive action of the gastric content. When, however, they were transplanted into defects made in isolated stomach pouches where they were exposed to the digestive action of the pure fundic secretion, they were promptly digested away.[7] One must conclude that, under normal conditions, the stomach is not digested away because it is not exposed to pure gastric juice or to a gastric content that approximates the pure fundic secretion in acid and pepsin concentration for any prolonged period of time. Food is the normal stimulus for gastric secretion and is probably also the chief factor which protects the mucosa from its corrosive action.

On theoretical grounds we might expect peptic ulcers to develop if gastric secretion is stimulated by agencies other than food, or when the secretion is so excessive that the buffering effect of the food is overcome. Both factors operate to produce chronic progressive ulcers in man. Duodenal ulcers appear when hypersecretion and hypermotility occur in the empty stomach as a result of excessive vagus stimulation.

Chronic peptic ulcers occur in the stomach, duodenum and jejunum of patients in association with specific types of tumors in the pancreas and duodenum described by Zollinger and Ellison.[45] These tumors secrete a substance, either identical with or very like gastrin, which enters the bloodstream and causes a continuous hypersecretion of gastric juice independent of food taking. While they are generally thought to take their origin from pancreatic islet tissue, it may well be that they arise from the cell that in the antrum normally secretes gastrin. Hyperparathyroidism and hyperinsulinism produced by functioning tumors of the parathyroid glands and of the beta cells in the pancreatic islets represent an analogous situation. Removal of the tumors abolishes the hypersecretion of gastric juice, and the ulcers heal.[35] They are, however, relatively rare and cannot account for many ulcers in man. Their great importance lies rather in the conclusive demonstration that a hypersecretion of gastric juice in man can produce a chronic progressive peptic ulcer in previously normal mucosa.

The sharply punched out appearance of the peptic ulcer in man undoubtedly suggested to Virchow the idea that these lesions are initially caused by an infarct in the mucosa. One puzzling aspect of the experimental ulcers in animals is also this sharply punched out appearance. How does pure gastric juice or an abnormally corrosive gastric content acting on the normal mucosa of the stomach or duodenum produce such a lesion instead of a widespread erosive gastritis or duodenitis? Of course a gastritis sometimes accompanies a duodenal ulcer (Konjetzmy [27]), but is usually not conspicuous. This is an unsolved problem. The observations of Watt in this connection are, however, of great interest.[42] Watt studied, with the microscope and by direct observation, the stomachs of guinea pigs given histamine and beeswax by intramuscular injection. Shortly after a vigorous

stimulation of gastric secretion was produced, oval or circular areas of pallor in the stomach wall could be seen which later on became perforating ulcers. If the gastric secretion was diluted or neutralized, these focal areas of pallor did not appear. In applying these findings to the clinical problem it appears entirely possible that the following sequence of events occurs. As the acidity of the gastric content approaches that of the pure fundic secretion, either as a result of hypersecretion or inadequate neutralization, the mucosa becomes increasingly irritated. Those areas most exposed would naturally be most irritated. The virtue of Watt's experiment lies in the demonstration that this acid irritation of the mucosa can produce a reflex spasm of an underlying arteriole with occlusion of the blood supply to a circular area of mucous membrane. The digestion of this area produces an acute lesion which progresses and becomes chronic only when the corrosive properties of the gastric content are greater than normal. In the presence of a normal gastric content, present evidence indicates that such a lesion would not result from simple vascular spasm.

## The Mechanism of Gastric Secretion

A consideration of the physiological mechanism which controls gastric secretion indicates that herein lies the principal reason why under normal conditions the stomach does not digest itself and produce a peptic ulcer. Recent work has made it possible to amplify somewhat the classical explanation of this mechanism. Under normal conditions, a constant or continuous secretion of gastric juice occurs in the empty stomach even though the individual is shielded from the sight, odor, or taste of food. The amount of acid in this secretion varies between ten and 20 mEq. in a 12-hour period at night, or a little over one mEq. per hour in the waking state. It is almost completely abolished by division of the vagus supply to the stomach, indicating

that it is chiefly of nervous origin. A marked augmentation in gastric secretion occurs with the ingestion of food, brought on first by secretory impulses in the vagus nerves aroused reflexly by the sight, odor, and taste of food. The entrance of food into the stomach further stimulates gastric peristalsis, which brings the food into contact with the antrum mucosa. Both contact of food with the antrum mucosa and antrum peristalsis cause a release of the hormone gastrin into the blood stream with stimulation of gastric secretion. It is likely that in many patients at the beginning of a meal, some neutral or faintly acid food escapes through the pylorus. This would cause the liberation of a gastrin-like hormone from the duodenal mucosa, and for a short time this intestinal phase of secretion would be operative. However, when the acidity of the gastric content reaches a pH of 2.5 to 3, further stimulation of gastric secretion ceases. This is brought about in two ways. When the food in contact with the antrum mucosa becomes acid as indicated above, experimental work in our laboratory [9, 30] has shown that gastrin ceases to be liberated from the antrum. The effect of acid on the antrum mucosa resembles that of cocaine in this respect. The evidence that acid in contact with the antrum mucosa causes the release of hormone into the blood stream which inhibits the secretion of gastric juice, is still incomplete and doubtful. When, however, the acid food passes into the duodenum, a humoral agent is released from the duodenal mucosa which inhibits gastric secretion. This humoral agent is probably pancreatic secretin, as the work from our laboratory indicating that secretin preparations inhibit gastric secretion [18] has been confirmed by Jordan and Peterson,[25] Kennedy and Hallenbeck [26] and Wormsley and Grossman,[44] using purer preparations of the hormone. It is thus quite evident that in normal people a complex mechanism exists which supplies large amounts of the highly corrosive and di-

gestant gastric juice at the proper time when food is in the stomach. This mechanism checks further secretion before the gastric content becomes sufficiently corrosive to damage the mucosa.

Acting on the concept that duodenal ulcers are usually caused by a hypersecretion of gastric juice of nervous origin, Dragstedt and Owens [10] in 1943 sectioned the vagus nerves to the stomach by a transthoracic operation. They had found that these patients secreted from three to ten times as much gastric juice in the empty stomach as did normal people, and, influenced by the experiments of Wangensteen and his associates, alluded to above, concluded that this hypersecretion was responsible for the ulcer and might be of nervous or vagus origin. They were gratified to find that following the vagotomy the fasting hypersecretion disappeared and the ulcers healed. However, gratification gave way to disappointment and concern when five of these early patients returned in a few years with new ulcers in the stomach, although the original duodenal ulcers remained healed and the nocturnal gastric secretion remained below normal values.[8] In the meantime, the necessity for the addition of a drainage procedure to vagotomy had become evident because of troublesome stasis of food in the stomach, gaseous distention, and diarrhea. Pyloroplasty of the Heineke-Mikulicz, Judd, and Finney types were first tried but with disappointing results, and finally a posterior gastroenterostomy of small size was adopted. This, together with decompression of the stomach for five days, proved successful in eliminating the immediate difficulties, and more significantly, stopped the appearance of gastric ulcers as a subsequent complication.

## The Pathogenesis of Gastric Ulcer

The concept that duodenal ulcers are caused by a hypersecretion of gastric juice of nervous origin is based upon the facts that these patients secrete three to ten

times as much gastric juice in the empty stomach as do normal people; that a hypersecretion of this degree will regularly cause the development of duodenal ulcers in experimental animals; that division of the vagus nerves to the stomach abolishes the hypersecretion; and that when vagotomy is combined with antrum resection or a drainage operation which prevents stasis of food in the antrum, the duodenal ulcers usually heal and remain healed. The development of gastric ulcers in patients after physiologically complete vagotomy supports the view [6] that these lesions are caused by a hypersecretion of gastric juice of humoral or hormonal origin. They cannot be due to a hypersecretion of nervous origin since the vagus nerves have been cut. Furthermore, experience demonstrated that gastroenterostomy was effective in preventing the subsequent appearance of gastric ulcers only when stasis of food in the antrum was prevented by placing the stoma within 5 or 6 cm. of the pylorus. In several cases a high-lying gastroenterostomy permitted such stasis in the antrum with ulcer recurrence. Woodward [43] recorded the appearance of gastric ulcers in two patients with gastric stasis following vagotomy and an inadequate pyloroplasty for duodenal ulcer.

In 1901 van Yzeran [41] discovered that division of the vagus nerves to the stomach in rabbits frequently caused the development of chronic gastric ulcers in these animals. These observations were confirmed by Auer [2] and by Beazell and Ivy.[3] We have recently repeated these experiments and in addition have tested the effects of gastroenterostomy and pyloroplasty when combined with vagotomy in rabbits. The details of this study will be published elsewhere.[28] In ten rabbits examined 90 days after vagotomy, chronic gastric ulcers were found in three, partially healed ulcers in two, and a large gastric diverticulum devoid of mucosa in one. In 12 rabbits examined 90 days after vagotomy and gastroenterostomy and in 12 with vagotomy and

TABLE 1. *The Effect of Vagotomy on Gastric Secretion in Patients with Gastrojejunal Ulcers After Gastric Resection for Duodenal Ulcers*

| Patient No. | HCl Output in the 12-Hour Nocturnal Gastric Secretion, in mEq. | |
|---|---|---|
| | Before Vagotomy | After Vagotomy |
| 1 | 39.8 | 0 |
| 2 | 10.0 | 0 |
| 3 | 72.8 | 0.6 |
| 4 | 89.0 | 1.0 |
| 5 | 136.0 | 0 |
| 6 | 38.7 | 0.9 |

pyloroplasty, no abnormalities in the gastric mucosa were found.

Further experimental evidence implicating gastric stasis in the pathogenesis of gastric ulcer was secured in dogs in which pyloric stenosis had been produced by cellophane tapes. The details of these experiments will also be published elsewhere.[5] In seven animals, where x-ray examination revealed gastric stasis, chronic gastric ulcers were found in three after a period of 70 days. In seven additional animals with pyloric stenosis, and which were also given daily injections of histamine in beeswax, chronic gastric ulcers appeared in four within a period of 27 days.

In 1955, Rigler, Oberhelman, Brasher, Landor and Dragstedt[36] reported that pyloric stenosis in dogs produced by this method caused a profound increase in gastric secretion, which was of hormonal origin since it was exhibited in Heidenhain pouches. Similarly, two groups of workers[15, 40] found that stasis of food in the stomach as a result of atony following vagotomy also caused marked stimulation of secretion from the Heidenhain pouch. This did not occur if the antrum had been removed or if a gastroenterostomy had been constructed to prevent stasis of food in the antrum.

A fairly extensive literature has accumulated regarding coexistent gastric and duodenal ulcers in man. This has been ad-

mirably reviewed by Harkins.[20] It is becoming increasingly apparent that in these cases the duodenal ulcer occurs first, producing pyloric stenosis with stasis of food in the stomach and a secondary gastric ulcer. This sequence of events was clearly demonstrated by Huber and Huntington in 1948.[23] These patients display the hypersecretion of gastric juice in the empty stomach so characteristic of the duodenal ulcer patient. We have found that both lesions heal very quickly after vagotomy and pyloroplasty or gastroenterostomy.[12]

Experience in the surgical treatment of gastric and duodenal ulcers lends support to the views developed as a result of the experimental studies referred to above. When gastroenterostomy or low partial gastric resection was employed in duodenal ulcer patients, gastrojejunal ulcers were not infrequent; however, when these operations were performed in gastric ulcer patients, gastrojejunal ulcers rarely occurred. We know now that excision of the antrum practically abolishes the humoral or hormonal phase of gastric secretion but has little effect on the nervous phase. Thus in duodenal ulcer patients the hypersecretion often continues unabated and a gastrojejunal ulcer develops. This is well-illustrated in Table 1, which shows the persistence of hypersecretion in the stumps of stomach remaining after partial gastrectomy in a group of patients with gastrojejunal ulcers after partial resection for duodenal ulcer. Considering the large size of the opening between the stomach and jejunum, it is surprising that such a large amount of secretion was obtained. Much must have been lost, and the figures probably represent only a portion of the actual secretion. Nevertheless, in several of the patients the amount of gastric juice aspirated in a 12-hour period was four to seven times the normal. Subsequent division of the vagi abolished the hypersecretion, providing final proof that it was of nervous origin, and the ulcers healed.

Resection of the lower part of the stomach in gastric ulcer patients is rarely followed by gastrojejunal ulceration. Indeed, the experience of surgeons [17] with the Kelling-Madlener operation indicates that excision of the antrum usually brings about healing of a high-lying gastric ulcer that has been left in situ. These facts support the view that the cause of these ulcers was hyperfunction of the antrum, and when this was removed the ulcers healed. It is possible that the few gastrojejunal ulcers which have been reported following partial gastrectomy for gastric ulcers may have occurred in patients with coexistent gastric and duodenal ulcers. These patients display a hypersecretion of gastric juice of nervous origin, which would persist after removal of the antrum, and so could cause a gastrojejunal ulcer. Studies of the fasting nocturnal secretion of gastric juice in these patients should be rewarding.

There has been recent discussion concerning the so-called channel ulcers which occur in the pyloric canal. Are they gastric or duodenal ulcers, and how should they be treated? It would seem more profitable to examine the fasting nocturnal gastric secretion in these patients, and so to classify the ulcers as being caused by a hypersecretion of vagus or of antrum origin. If the fasting secretion is abnormally great, vagotomy should have the leading place in definitive treatment, regardless of the location of the ulcer. In this connection, if the output of free acid in the 12-hour nocturnal secretion exceeds 100 mEq., the probability of a tumor of the Ellison-Zollinger type being present in the pancreas or duodenum is very real. It is almost certainly present if the output of acid in the empty stomach is not reduced by more than one-third by anticholinergic drugs such as Pro-Banthine. If the fasting nocturnal secretion is less than normal, these ulcers should be treated as gastric ulcers, that is, as ulcers caused by a hypersecretion of gastric juice of gastrin origin.

## Comments on the Treatment of Gastric Ulcers

Several years ago the proposal was made that all chronic ulcerating lesions in the stomach be treated by subtotal gastric resection. This plea arose because in the experience of many surgeons from 5 to 20 per cent of stomach specimens resected for benign ulcer were found on microscopic examination to be cancers. It was hoped that the result of such a program would be the removal of many gastric cancers at an earlier stage in their development, hence a better prospect for cure of the disease. The proposal was not, however, widely accepted. The gastroenterologist felt that his error in diagnosis was much less than that indicated by the surgeons, and he countered with the observation that the mortality of subtotal gastric resection for cancer was in the neighborhood of 5 to 7 per cent; that the morbidity was often considerable; and that, furthermore, gastric resection was not a very good operation anyway, since only 5 to 10 per cent of patients with gastric cancer were cured by surgery. Since the surgeon could not assure him that all patients who might die from subtotal resection for an ulcerating lesion had cancer and so would die anyway, the argument lost considerable force. The internist knew that medical treatment was fairly effective for benign gastric ulcer and was reluctant to subject his patient to the hazards and sequellae of gastric resection. However, the frequently repeated recurrences of gastric ulcers treated by various medical regimes, coupled with the fact that a significant but variable proportion of them are cancers, indicate the limitations of medical treatment.

Possibly the proposal made recently by Dragstedt and Woodward [21] would prove more acceptable. Once the diagnosis of gastric ulcer is made, the nocturnal gastric secretion determined, and the presence or absence of stasis in the stomach ascer-

tained by x-ray examination eight to 12 hours after the patient has taken a meal, he should be referred for immediate operation. The Surgeon then undertakes to explore the stomach and perform a biopsy on the regional lymph glands. The stomach is opened and the ulcer is visualized and palpated with the ungloved hand. A punch biopsy specimen is secured from each quadrant of the ulcer and from any additional suspicious area. If microscopic examination reveals the presence of carcinoma, a full-scale cancer operation is performed. If no cancer is detected, the gastrotomy is closed and a vagotomy combined with antrum resection, pyloroplasty, or gastroenterostomy is done.

It must be admitted that an occasional cancer will be missed by such a procedure, but resection of the stomach in all ulcer patients is not justified for this reason alone—the mortality and morbidity are too great. However, it remains to be seen if the conservative operation for gastric ulcer will prove as successful as resection. There is good reason to believe that it will. The analysis of the pathogenic factors in gastric ulcer presented in this paper supports the view that these lesions are usually caused by stasis of food in the stomach as a result of atony or pyloric stenosis. Stasis does not stimulate gastric secretion unless the antrum is present. There is thus a logical reason for antrum resection or a drainage procedure. Should vagotomy be done in addition?

When vagotomy was first employed for the treatment of peptic ulcer in our clinic, we did not appreciate the differences in gastric and duodenal ulcers; these distinctions have subsequently become evident. For this reason, eight patients with chronic gastric ulcers were treated by vagotomy alone or by vagotomy combined with gastroenterostomy.[21] Three of these patients had coexistent duodenal ulcers. Two were treated by vagotomy alone and one was treated by vagotomy combined with gastro-

enterostomy. In all three patients the ulcers healed promptly, as evidenced by x-ray examination or gastroscopy. Large gastric ulcers in three of the remaining five patients healed promptly after vagotomy alone, but in two patients with similar gastric ulcers very little healing was observed.

It seems clear that stasis of food as a result of gastric atony following vagotomy is a potent factor in the genesis of gastric ulcer. The mechanism of this appears to be long-continued stimulation of gastric secretion by means of gastrin released from the antrum. If the antrum is removed or if stasis of food in the stomach is prevented by an adequate drainage operation, would vagotomy under these conditions contribute to the healing of a gastric ulcer and to the prevention of recurrence? There is some evidence to suggest that under these conditions vagotomy would be helpful. Several years ago, Oberhelman and Dragstedt[34] found that both dogs and man secreted from one-third to one-fourth as much gastric juice in response to a standard dose of histamine after vagotomy as they did when the nerves were intact. A similar decreased sensitivity of the gastric glands to the stimulating action of gastrin was found by Grossman and Andersson[19] when Pavlov pouches were converted into Heidenhain pouches. In addition to this decreased response of the gastric glands to humoral stimuli, vagotomy of course removes the nervous phase of gastric secretion, although this is usually not great in gastric ulcer.

Recently several investigators have concluded, as a result of experimental studies on animals, that vagus impulses directly activate the cells that manufacture gastrin. Evidence for this view has recently been summarized by Schofield.[37] While we are somewhat doubtful of the existence and significance of this effect, it is of course obvious that vagotomy would eliminate this so-called vagal release of gastrin. There is thus some reason to expect that vagotomy

plus antrectomy or a drainage procedure will be more effective than either of these procedures alone.

## Gastric Stasis in Gastric Ulcer Patients

Stasis of food in the stomach of those patients with coexistent gastric and duodenal ulcers with pyloric stenosis has been clearly demonstrated.[23] Evidence is likewise sufficient to indicate that patients who develop gastric ulcers after vagotomy alone have prolonged gastric stasis due to relative gastric atony. In both situations experimental data indicate that a long-continued hypersecretion of gastric juice of hormonal origin occurs. The question remains: Do patients with gastric ulcer but without a preceding duodenal ulcer or pyloric stenosis likewise have stasis of food in the stomach? These patients display a fasting nocturnal secretion of gastric juice which is usually less than normal. Since the fasting secretion is chiefly of nervous origin, this finding suggests that the secretory tonus of the vagus nerves is decreased. Is the vagus effect on the tonus and peristalsis of the stomach in gastric ulcer patients also less than normal, thus producing a relative gastric atony resembling that after vagotomy?

In the paper alluded to above [24] Hurst states that, "More recently it has become recognized that the stomach in cases of gastric ulcer is generally somewhat hypotonic, and almost invariably empties itself more slowly than the average normal." In contrast, the stomach in duodenal ulcer patients is usually hypertonic. Similar views have subsequently been expressed for the most part in roentgenologic literature. Thus, in 1931, Emery and Monroe [14] stated that gastric retention occurs in 50 per cent of cases of gastric ulcer. Bull [4] concluded that the delayed emptying time of the stomach in gastric ulcer must be due to inhibition of peristalsis, since pyloric obstruction usually could not be demonstrated.

More data are clearly needed to determine the existence and frequency of gastric atony and delayed gastric emptying in gastric ulcer. Such data should be secured by giving the patient a meal of his customary type to which barium has been added. X-ray examination should then be made at intervals up to 24 hours to determine when the last bit of food has left the stomach. Six patients with gastric ulcers and sub-normal fasting secretion have been studied in our clinic by this method, and all of them have displayed delayed emptying. In one patient, food was still present in the stomach 24 hours later.

## Summary

Evidence presently available indicates that the gastric content of man becomes sufficiently corrosive to break down the normal mucosa and produce a chronic peptic ulcer when gastric secretion is stimulated by agencies other than food, or when hypersecretion occurs. The evidence that gastric ulcers are usually caused by a hypersecretion of gastric juice of hormonal or gastrin origin due to stasis of food in the stomach is steadily becoming more impressive. Pyloric stenosis in man as a result of a duodenal ulcer sometimes causes the development of a secondary gastric ulcer. Both lesions may heal rapidly after vagotomy and a drainage operation. Chronic gastric ulcers were produced in dogs by causing pyloric stenosis with cellophane tapes. Stenosis of the pylorus produced in this way caused a hypersecretion of gastric juice in Heidenhain pouches. Vagotomy alone in man and rabbits often causes prolonged gastric stasis and is sometimes followed by the development of chronic gastric ulcers. Vagotomy combined with antrum resection or with an adequate drainage operation, such as pyloroplasty or gastroenterostomy, is rarely or never followed by gastric ulceration in man or rabbits.

Hyperfunction of the antrum with hypersecretion and typical ulcer formation can

be induced in dogs by transplanting the antrum into the colon. In an analogous way, exclusion of the antrum from contact with the acid gastric content, as in the Finsterer-Devine type of gastric resection, is often followed by gastrojejunal ulceration. Antrum resection or gastroenterostomy was often followed by gastrojejunal ulceration when performed for duodenal ulcer, but rarely when performed for gastric ulcer. The fasting gastric secretion is abnormally great in duodenal ulcer patients, persists after antrum resection or a drainage procedure, and is probably the cause of the new gastrojejunal ulcer. This hypersecretion is abolished by vagotomy, indicating that it is of nervous origin. The fasting secretion in gastric ulcer patients is less than normal, suggesting that the vagus tonus in these patients is decreased. The rarity of gastrojejunal ulcer after antrum resection for gastric ulcer, and the beneficial effect of this procedure on the healing of gastric ulcers left *in situ* (the Kelling-Madlener operation) are in harmony with the view that prolonged liberation of gastrin is the cause of these lesions.

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## DISCUSSION

PROFESSOR D. J. DU PLESSIS (Johannesburg, Republic of South Africa): I have been particularly interested in Dr. Dragstedt's stimulating address because we have been engaged in the study of this problem for many years.

We could find no evidence of an increased secretion of gastrin or acid in patients with gastric ulceration, and we consequently assumed that gastric ulceration was the result of a defect in the resistance of the gastric mucosa to normal secretion.